

EDITORIAL COMMENT

Exercise Testing in Heart Failure

Maximal, Submaximal, or Both?*

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Heart failure (HF) due to systolic dysfunction is a highly prevalent and often lethal condition, despite recent advances in pharmacologic therapy. Cardiac transplantation as a therapeutic modality is severely limited by organ availability. Exercise testing has been used for some time to determine patients' functional status, to assess response to therapy, to determine prognosis, and, in those with advanced stages of disease, to aid in the selection of appropriate candidates for transplantation. Considerable controversy persists, however, about what type of exercise protocol best predicts prognosis, how results from different types of exercise testing relate to each other, and which specific exercise parameters have the most prognostic utility. Recommendations for prognostication have ranged from simple dichotomous classifications of oxygen consumption (VO_2) above or below certain cut-off values to use of complex prognostic scores (1,2).

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Exercise testing and prognosis. Maximal cardiopulmonary exercise testing is considered to be the gold standard of assessment of functional capacity and prognosis in patients with HF. Numerous studies document a relationship between maximal or peak VO_2 adjusted for body weight or lean body mass and subsequent mortality (1–8). This relationship is independent of routinely recorded clinical patient characteristics known to influence prognosis, such as age, gender, etiology of HF, left ventricular ejection fraction, or New York Heart Association classification, but it may no longer be significant when neurohumoral measures are added to the models (7,8). Different investigators have recommended different threshold values of peak VO_2 for prognostic classification (1,3–5). It is thus clear that there is no single value that discriminates between “good” and “poor” prognosis and that it may be better to use peak VO_2 as a continuous variable. Percent predicted VO_2 , by virtue of adjusting for age, weight, and gender, may be an even better indicator of prognosis than peak VO_2 , especially among women (9,10). Many other parameters that can be directly measured during traditional cardiopulmonary exercise testing or can be derived from measured parameters also relate to prognosis, including: exercise duration and workload; the

ventilatory response (expressed as the slope of minute ventilation and carbon dioxide output); estimates of cardiac power (peak VO_2 multiplied by systolic blood pressure [BP]); chronotropic response and heart rate recovery; and time course of recovery of oxygen uptake after exercise (11). These may provide incremental value when added to measurement of peak VO_2 , but their role in the routine clinical assessment of patients remains unclear.

Maximal cardiopulmonary exercise testing is often difficult for patients (especially those who are very ill, severely deconditioned, or elderly), equipment for testing is expensive and requires regular maintenance, special expertise is required for the interpretation of the exercise studies, and the maximal exercise performed does not relate to patients' day to day activities. Maximal cardiopulmonary exercise testing, thus, may not be suited for many outpatient settings. Submaximal exercise testing has been suggested as an alternative. The 6-min walk test as originally described by Guyatt et al. (12) has been widely used to assess submaximal exercise capacity in patients with HF. Its role in assessment of prognosis remains controversial. Several research groups have shown that the 6-min walk test predicts morbidity and mortality in patients with varying severity of HF, whereas other investigators found VO_2 measurement to be superior or could not demonstrate any relationship between walked distance and prognosis (13–19). Differences in walking protocol, patient selection, and length of follow-up likely account for some of this heterogeneity. Measurement of VO_2 during the 6-min walk test has shown that many individuals with more advanced HF achieve anaerobic threshold and that VO_2 during the walk is on average only 15% lower than during maximal testing (20). Submaximal testing may thus be sufficient and preferable for patients with very poor exercise capacity, whereas traditional maximal exercise testing may better discriminate prognosis among patients with more preserved functional capacity.

The current study. In this issue of the *Journal*, Rickli et al. (21) suggest that submaximal and maximal cardiopulmonary exercise testing can be easily combined in a single test and that such combined testing provides more powerful prognostic information in patients with HF than either test alone. They evaluated exercise test results and outcomes in 202 patients (86% men) who had been referred to their clinic for possible cardiac transplantation. All patients underwent a two-stage exercise test (6 min of walking on a treadmill at 1.0 mph with an elevation of 6%, followed by graded exercise testing with gas exchange analysis with workload increase of approximately 0.15 W/kg body weight/min until exhaustion). Mean follow-up was 873 days. Impaired oxygen kinetics during submaximal steady state exercise expressed as a mean response time >50 s, peak $\text{VO}_2 < 50\%$ predicted, and resting systolic BP < 105 mm Hg provided complementary prognostic information. Patients with none or one of these risk factors had a one-year event rate of 3%; those with two risk factors had a one-year

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event rate of 33%; and among the 13 patients with all three risk factors, the one-year event rate was 59%. The prognostic utility of these factors was apparent both in patients receiving and in those not receiving therapy with beta-blockers.

Slowed oxygen uptake kinetics during the early stages of exercise in patients with circulatory abnormalities were first reported in the 1920s and have been confirmed by several groups of investigators since (22–26). Mean response time and oxygen deficit measured during submaximal steady state exercise on one hand and peak VO_2 on the other correlate with patients' symptoms, but they correlate only moderately with each other (26). Measurement of mean response time is likely to be more reproducible than measurement of peak VO_2 because it is not dependent on patient effort and may be more closely related to functional limitations during activities of daily living. Mean response time appears to be more closely related to a patient's neurohormonal status (e.g., levels of norepinephrine, atrial natriuretic factor, brain natriuretic peptide) than peak VO_2 (26). This close correlation with neurohumoral activation may in part account for its prognostic utility.

Zugck et al. (27) described the impact of beta-blockade on the prognostic utility of variables customarily used for risk stratification in HF. Peak VO_2 was predictive both in patients receiving and in those not receiving beta-blocker therapy, but those with peak VO_2 below 14 ml/kg/min who were receiving beta-blocker therapy had a prognosis indistinguishable from those with higher VO_2 who did not receive beta-blocker therapy. Beta-blockade would also be expected to affect the prognostic utility of submaximal exercise parameters because it slows oxygen uptake kinetics (25). Rickli et al. (21), in the current study, found similar prognostic value of their combined assessment of prolonged mean response time, lower peak oxygen uptake, and low systolic BP both in patients receiving and in those not receiving beta-blocker therapy. However, as shown in their Figure 4, actual survival rates free of urgent transplantation in the low and intermediate risk groups were substantially better among those treated with beta-blockers, suggesting that any risk assessment algorithm used clinically should stratify on beta-blockade. It is interesting that beta-blocker therapy did not seem to impact outcome in the highest-risk group, but this null result may have been a result of the very small number of patients in this risk stratum.

The current study included few women, few older individuals, no non-Caucasians, and no patients with non-cardiac exercise limitations; all patients were specifically referred for cardiac transplant evaluation. It is thus unclear whether the results can be applied to other patient groups and less specialized patient care settings. Furthermore, submaximal exercise capacity as measured by 6-min walk distance appears to be greater in European than in American populations at any given severity of HF, possibly because of different levels of customary physical activity (28). Activity levels and exercise training have been shown

to alter oxygen uptake kinetics during submaximal exercise (25). It is thus possible that there are also "transatlantic" differences in mean response time and oxygen deficits that may affect the prognostic utility of these variables.

Combining results from submaximal and maximal exercise testing for prognostication is based on sound pathophysiologic rationale. Such combined testing does not add to a patient's burden when compared with traditional maximal exercise testing and is feasible in any setting in which cardiopulmonary exercise testing equipment and trained personnel are available. Although the preliminary results by Rickli et al. (21) are intriguing, prospective studies in large, heterogeneous patient populations are needed to more clearly determine applicability of these preliminary findings in various patient subgroups and different patient care settings.

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